REMARKS

Claims 1-11 and 13-14 are pending in this application and have been rejected by the Examiner. Claim 12 was previously cancelled. Claims 15-30 have been cancelled to remove the non-elected invention. Claim 1 has been amended to add "C_{1-4}alkyl ester" in front of the term "prodrug". Support for such amendment may be found on page 5, paragraph [0096] of the published specification (2006/011400). Claims 1 and 14 have been amended to further clarify the claims by adding the (R) and (S) notation to the chemical structure. This notation is inherent in the structures as drawn in the original and current claims. Such notation can also be found in the examples in the specification. Claim 1 has also been amended to add a dash in front of "alkylAr^1" so as to read "-alkylAr^1". This amendment is to correct an obvious mistake as it can be seen in the examples that Applicants intended for the ring-nitrogen to be substituted with alkylaryl wherein the substituent is connected via the alkyl group. Claim 11 has also been amended to add "in free, pharmaceutically acceptable salt or C_{1-4}alkyl ester prodrug form. Support for such amendment may be found in original claim 11 and on paragraph [0092] of the specification. Other amendments have been made to correct typographical errors. It is believed no new matter has been added.

Restriction Requirement

Previously, the Examiner restricted the claims thirteen ways, arguing that U.S. Patent 4,639,436 (Junge et al.) anticipates the claimed compounds of Group I and therefore does not meet the unity of invention requirement. *Office Action* dated 7/28/2008, p. 4. The Examiner also argued that the structural formula of the compounds of the current invention includes the dotted ("----") and the wedged ("▬") configurations, which denotes the up and down configuration from the ring, rather than the well recognized "R" and "S" configuration and therefore does not limit the claimed compounds to a specific stereochemistry. *Office Action* dated 12/8/2009, p. 2. The Examiner, therefore, concluded that the claims are without stereo limitations and as such are anticipated by Junge et al. and as such made the restriction requirement final. Without agreeing as to the accuracy of the Examiner's statement, Applicants cancelled non-elected claims 15-30 with

traverse, reserving the rights to pursue cancelled subject matter in a divisional and/or continuation application.

Rejection under 35 *U.S.C.* § 112, Second Paragraph

The Examiner maintained the rejection of claims 1-10 and 13-14 for being indefinite, arguing that the doted and wedge notation does not offer any stereo limitation. To avoid any doubt and to expedite allowance of the claims, Applicants have amended claims 1 and 14 to specify the stereochemistry of each chiral carbon on the ring of the claimed compounds. It is believed that the amendment will overcome the Examiner's rejection under section 112, second paragraph. Reconsideration and withdrawal of the rejection under this section is earnestly requested.

Rejection under 35 *U.S.C.* § 112, First Paragraph

The Examiner maintained the rejection of claims 1-11 and 13-14 for failing to comply with the enablement requirement, arguing that the specification does not provide "sufficient information as to what kind of modification of the drug functional groups to provide an inactive prodrug which will be released into the active form in vivo." *Office Action* dated 12/8/2008, p. 3. The Examiner further argued that prodrugs are not active, but because U.S. Pat. No. 5,003,072, col. 21, table 1 shows that hydroxy and acylated hydroxy compounds have biological activity, "the acylated compounds [of the current invention] are not 'inactive' prodrugs of the non-acylated compounds." *Office Action* dated 6/3/2009, page 3, ¶ 4.

Applicants have amended claim 1 to add "C_{1-4}alkyl ester" in front of the term "prodrug". Applicants respectfully submit that the specification is enabling for such prodrugs of the claimed compounds as one skilled in the art would know what prodrugs are possible, e.g., for the hydroxy substituents and how to make such prodrugs so as to allow a skilled artisan to make and use the invention. As such, C_{1-4}alkyl esters formed with the claimed compounds of the invention, for example, wherein the hydroxy substituent of the compound of the invention (e.g., drug-OH) forms an alkyl ester with the hydroxy substituent (e.g., drug-O-**C(O)-C_{1-4}alkyl**) are enabled by the invention.

The Examiner argued that various ester compounds disclosed in Table 1 of the 5,003,072 (the '072 Patent) have biological activities, and as such, the acylated claimed compounds (i.e.,

ester prodrugs) are not "inactive" prodrugs. Applicants respectfully disagree. None of the Examples disclosed in the '072 Patent falls under the scopes of the claimed invention as they do not have aryl or -alkylaryl substituents on the ring-nitrogen. It is improper to impute the activities of the compounds of the '072 patent onto the compounds of the current invention just because there are similarities in the two chemical formulas. Applicants respectfully submit that the Examiner has not shown that the claimed prodrugs of the compounds of the invention have biological activities. Even if the corresponding ester (i.e., acylated) prodrug compounds of the current invention are biologically active, Applicants respectfully submit this does not necessarily render them unfit as a prodrug. Unlike MedicineNet.com, a website cited by the Examiner which provides information to consumers, an article in the *Mini-Reviews in Medicinal Chemistry*, a journal designed for medicinal and pharmaceutical chemists, defines prodrug as "being inactive or much less active than the drug and must be hydrolyzed by chemical or enzymatic means, releasing the active molecule." Silva et al., Advances in Prodrug Design", *Mini-Reviews in Medicinal Chemistry*, 2005, 5:893-914, 895, second column (emphasis added)(submitted herewith). In another article, *J. Med. Chem.*, 2007, 50(15):3743-3746, the authors discuss the synthesis and biological activity of a Gemcitabine phasphoramidate prodrug, noting that "the prodrug was about an order of magnitude less active than gemcitabine against wild-type cells ", but "[t]he prodrug was more active than gemcitabine against two deoxycytidine kinase-deficient cell lines." *Id.* at abstract (submitted herewith). These articles therefore support Applicants' position that just because a compound has some biological activities does not render it unfit for a prodrug. Therefore, whether the prodrugs of the claimed compounds have biological activities or not would not necessarily disqualify them as prodrugs. Applicants respectfully request the Examiner to reconsider and withdraw the rejection under Section 112, First Paragraph.

Rejection under 35 *U.S.C.* § 102(b)

The Examiner rejected claims 1-11 and 13-14 for being anticipated by Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093, RN 141206-38-4; Brock et al. CA 119:96007, RN 149302-52-3, RN 149302-53-4; Berg et al. RN 8117-43-3; Kurihara et al. CA 114:185939 RN 1333342-47-9, under 35 *U.S.C.* § 102(b) based on the conclusion that the claimed compounds do

not contain any stereo limitation. *Office Action* dated 6/3/2009, ¶ 5. Applicants' amendment of the claims to add the (R) and (S) notation should overcome the rejection under section 102 as Boeschagen et al., CA 113:126581; Broek et al., CA 119:96007; Kurihara et al., CA 114:185939 and Berg et al., CA 96:117597 (the search results cited by the Examiner) all disclose compounds having a (2R, 3R, 4R, 5S) configuration, and Ezure et al., CA 116:236093 discloses compounds having a (2R, 3S, 4R, 5S) configuration, all of which differ from the (2S, 3S, 4R, 5S) stereo limitation of the claimed invention. Because the art references cited by the Examiner do not disclose a compound having the stereo configuration and the ring-nitrogen substituents as the claimed invention, they fail to be anticipatory. Reconsideration and withdrawal of the rejections under Section 102 are respectfully requested.

Rejection under 35 *U.S.C.* § 103

The Examiner maintained the rejections of Claims 1-11 and 13-14 under 35 *U.S.C.* § 103(a) as allegedly being obvious over Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093, RN 141206-38-4; Broek et al. CA 119:96007, RN 149302-52-3, RN 149302-53-4; Berg et al. RN 8117-43-3; Kurihara et al. CA 114:185939 RN 1333342-47-9 in view of U.S. Patent 5,051,407, U.S. Patent 7,256,005 and Kato et al., *J. Med. Chem.* (2005) 48:2036-2044. In relying on the introduction statement in Kato et al. which states that "azasugars (iminosugars) are an important class of glycosidase inhibitors and are arousing great interest as potential therapeutic agents such as antidiabetics, antiobesities, antivirals, and therapeutic agents for some genetic disorders" and the disclosure in U.S. Pat. 5,276,120 col. 2, lines 9-25 that deoxyazasugar is known as a class of compounds with biological activities, the Examiner argued that "when a lead deoxyazasugar is found with biological activity, one can modify the stereo-configuration with other saccharides with the expectation that it will have biological activity." *Office Action* dated 6/3/2009, page 4, ¶ 6.

Applicants respectfully disagree. Just because a compound is disclosed broadly as a class of compounds having some biological activities does not render every compound within that class obvious and unpatentable. Azasugar is a large class of 6-membered, 5-membered as well as 7-membered rings, mono and/or poly hydroxylated, having different stereo configurations and

different substituents on the ring-nitrogen. According to the Examiner, disclosure of azasugars as a class of compound known to have biological activities would render all of these compounds unpatentable as they all would be obvious in view of the disclosure. This standard is in stark contrast to the Federal Circuit's requirement to identify the lead compound, stating that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general begins with the reasoned identification of a lead compound". *Eisai Co. v. Dr. Reddy's Lab.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008), Similarly in *Takeda Chem. Industries, Ltd. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), the Federal Circuit specifically states that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure" *Id.* at 1356. The Court went on to clarify: "[a] known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.' [(citation omitted)] We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.". *Id.* (citations omitted).

Here, the Examiner identified azasugar as a class of compounds having biological activities and cited different arts which disclose various stereo configurations, but has not identified where in the art that suggests one stereo configuration is preferred over the other or why the (2S,3S,4R,5S) 6-membered ring azasugar is the lead compound. In addition, the Examiner has not shown where in the art that suggests that aryl or -alkylaryl substitution on the ring-nitrogen is preferred out of the numerous substituents disclosed so as to identify an aryl or - alkylaryl substituted azasugar compound as being the lead compound. As can be seen (in hindsight) in Tables 2 and 3 of Kato et al., L-*ido*-DNJ and L-*manno*-DNJ are not active against any enzyme at all and would not be an alternative choice for D-*manno*-DNJ or D-*ido*-DNJ as one isomer has inhibitory activities against specific glycosidases while the other isomer does or may not have inhibitory activities at all. Therefore, it is difficult to rationalize, in hindsight, the inhibitory activities of the various enantiomers of imino sugar compounds, let alone predict the activity of an

enantiomer against a particular enzyme. Given the unpredictability of activities of sugar and sugar mimetic compounds, one skilled in the art would not expect that all of the stereoisomers are active against a certain enzyme and therefore would not be motivated modify the prior art compounds and still have an expectation of success. It is only with hindsight knowledge of the current invention is the Examiner able to identify the (2S,3S,4R.5S) 6-membered ring azasugar or an aryl or - alkylaryl substituted azasugar compound as a compound of choice, which is impermissible. Applicants, therefore, respectfully submit that the Examiner has not met her burden of proving prima facie obviousness.

Provisional Obviousness Type Double Patenting Rejection

The Examiner rejected Claims 1-11 and 13-14 on the ground that the claims of the present invention are allegedly unpatenable over the claims of copending Application No. 10/522,208 (hereinafter "the '208 Application) or 10/586,188 (hereinafter "the '188 Application) in view of U.S. 5,051,407 or EP 536 402 and Brine et al. or Kato et al. as being barred by the non-statutory obviousness-type double patenting. The Examiner argued that "Applicants neither demarcated the scope of the copending claims nor filed acceptable terminal disclaimer."

In view of the current amendment to the claims, adding the (R) and (S) notation to the formulas, clearly distinguishing the currently claimed invention from the claims of the '208 and the '188 Applications, which are directed to azasugar derivatives having stereochemical configurations which are different from the compounds of formula (I) of the present invention, Applicants respectfully request reconsideration and withdrawal of the provisional obviousness-type double patenting rejections. Applicants again note that there is nothing predictable about the biological activities of chiral compounds as can be seen in Kato et al. and the Butters et al. (discussed and argued in Applicants' response to the previous office action) since one enantiomer of the azasugar may be significantly more selective against a specific therapeutic activity than another enantiomer of that compound. Accordingly, the disclosure of activity and/or toxicity of one enantiomeric compound would not render obvious the activity and/or toxicity of the other enantiomer. Therefore, the claimed compounds of the current invention are unobvious and patentably distinct from those claimed in the '208 and the '188 Applications. As such, Applicants

respectfully request the withdrawal of the obviousness-type double patenting rejection.

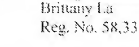
Applicants again further note that the later filed case ('188 Application) has not even been examined, let alone issued as a patent nor have claims been allowed in this case nor in the '208 case. As none of these applications have allowable claims, Applicants respectfully submit that the obviousness-type double patenting rejection is premature and respectfully requested that this rejection be addressed upon allowance of claims in at least one of the applications.

9. CONCLUSION

In summary, compounds of different stereochemistry, particularly sugars and sugar mimetics, may have completely different binding and/or biological activities as can be seen in Kato et al. and Butters et al. (discussed in Applicants' previous response). The teaching of one stereoisomer as being biologically active would deter rather than motivate one skilled in the art to synthesize the other isomer, as there is no reason to expect the other compound to have the same activity, selectivity, or toxicity profile due to their unpredictable nature. Therefore, Appellants respectfully request that rejections of the pending claims be withdrawn.

As this response is filed within two-months from the mailing date of the Final Office Action dated June 3, 2009, which response is due September 3, 2009, it is believed no fee is required. Should this be incorrect, the Commissioner is authorized to charge any additional fees, or credit any overpayment, to deposit account No. 50-4255.

Respectfully submitted,

Date August 3, 2009 By 

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